

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 16:37:49 ON 11 MAR 2011

L1 3164 S (RETRO? OR LENTI?) (P) ((THYMIDINE KINASE) OR (TK))  
L2 112 S L1 (P) IRES  
L3 9 S L2 AND HIV?  
L4 3 DUP REM L3 (6 DUPLICATES REMOVED)  
L5 2898 S (RETROVIR? OR LENTIVIR? OR MULV OR MLV) (P) ((THYMIDINE KINASE) OR (TK))  
L6 135 S L5 AND IRES  
L7 68 DUP REM L6 (67 DUPLICATES REMOVED)  
L8 43 S L7 AND PD <= 2003

AU Kim, Seon-Young; Lee, Chang-Hun; Kim, Kyung-Joo; Kim, Yeon-Soo  
SO Journal of Microbiology and Biotechnology (2001), 11(2), 234-241  
CODEN: JOMBES; ISSN: 1017-7825

TI Expression of the functional recombinant interleukin-16 in E. coli and mammalian cell lines

AB The C-terminal 393 bp region of the human interleukin-16 (IL-16) gene was cloned and expressed in Escherichia coli along with mammalian cell lines. Recombinant IL-16 expressed from E. coli was 22 kDa on SDS-PAGE and showed 260% of chemoattractant activity at a concn. of 0.1 .mu.g/ml. HeLa, COS, and Neuro-2a cells were transduced by recombinant retrovirus vector pLNC/IL-16/IRES/TK and the intracellular and secreted amts. of IL-16 produced by HeLa/IL-16/TK, COS/IL-16/TK, and Neuro-2a/IL-16/TK cells were detd. by ELISA. HeLa/IL-16/TK (1.times.105) and COS/IL-16/TK (1.times.105) cells secreted 36.1 and 13.3 ng of IL-16 for 48 h, resp. Forty-nine ng and 86.4 ng of IL-16 remained in the cell lysates of HeLa/IL-16/TK and COS/IL-16/TK. Intracellular and secreted amts. of IL-16 from Neuro-2a/IL-16/TK (5.times.105) cells during 24 h cultivation were 50 ng and 3.3 ng, resp. Also, HeLa and COS cells were stably transfected with mammalian expression vector pCRIII/IL-16. Both culture media and cell lysates prepd. from HeLa/IL-16 cells and COS/IL-16 cells showed chemoattractant activity ranging from 190% to 460% as compared to the control expt. Expression of the herpes simplex virus thymidine kinase (HSV-tk) gene in pLNC/IL-16/IRES/TK bicistronic retroviral expression vector was verified by performing a ganciclovir (GCV) sensitivity assay. Finally, IL-16 repressed Tat-transactivated human immunodeficiency virus type 1 long terminal repeat (HIV-1 LTR) promoter activity.

AU Marcello A; Giaretta I  
SO Research in virology, (1998 Nov-Dec) Vol. 149, No. 6, pp. 419-31.  
Journal code: 8907469. ISSN: 0923-2516. L-ISSN: 0923-2516.

TI Inducible expression of herpes simplex virus thymidine kinase from a bicistronic HIV1 vector.

AB The possibility of protecting human CD4+ lymphocytes from human immunodeficiency virus type 1 (HIV1) infection, through a suicide mechanism elicited by the HIV1 transcription apparatus itself, offers a potentially useful approach for gene therapy of the acquired immunodeficiency syndrome. A replication-defective lentiviral HIV1 vector (HYIRES-TK) was designed to carry both the hygromycin (Hy) phosphotransferase gene for positive selection and the thymidine kinase (TK) gene of herpes simplex virus driven by the viral long terminal repeat (LTR). The internal ribosome entry site (IRES) from encephalomyocarditis virus was placed between the two genes for their efficient simultaneous translation. Transient expression of active TK into transfected COS-1 cells was shown to be induced by Tat and Rev over a detectable basal level. By providing the missing viral proteins in trans, recombinant viruses were generated and used to

transduce Jurkat cells. The Hy-resistant population of cells was sensitive to ganciclovir (GCV) and acyclovir (ACV), a result consistent with a basal level of TK expression. Cocultivation of transduced cells with cells chronically infected with HIV in the presence of 10 microM ACV, a concentration non-toxic for the uninfected cells, resulted in increased killing of cells transduced with the HY-IRES-TK vector. These data indicate that two genes can be expressed from the viral LTR in the context of an HIV1 vector, with the aid of an IRES sequence. The expression is inducible by the HIV proteins Tat and Rev and it is possible to specifically kill infected cells with subtoxic concentrations of drug. To decrease the sensitivity of the transduced cells towards GCV, a variant vector expressing a truncated TK was constructed. The truncated version was expressed at levels similar to those of wild-type TK but induced sensitivity towards GCV in transduced cells that was intermediate between that of untransduced cells and of cells expressing wild-type TK.

AU Sugimoto Y; Sato S; Tsukahara S; Suzuki M; Okochi E; Gottesman M M; Pastan I; Tsuruo T

SO Cancer gene therapy, (1997 Jan-Feb) Vol. 4, No. 1, pp. 51-8.

Journal code: 9432230. ISSN: 0929-1903. L-ISSN: 0929-1903.

TI Coexpression of a multidrug resistance gene (MDR1) and herpes simplex virus thymidine kinase gene in a bicistronic retroviral vector Ha-MDR-IRES-TK allows selective killing of MDR1-transduced human tumors transplanted in nude mice.

AB Ha-MDR-IRES-TK is a bicistronic vector that coexpresses the MDR1 gene and the herpes simplex virus thymidine kinase (HSV-TK) gene. In the present study we examined the effect of ganciclovir on MDR1-positive tumors that have been transduced with Ha-MDR-IRES-TK. To establish a human tumor xenograft model of MDR1-transduced recurrent tumors, human KB-3-1 carcinoma cells were transduced with HaMDR or Ha-MDR-IRES-TK, and one each of representative clones, termed KB/MDR and KB/MDR-TK, respectively, were isolated. KB/MDR and KB/MDR-TK showed similar levels of multidrug resistance in vitro. Vinblastine strongly inhibited the growth of the parental KB-3-1 tumors in nude mice but showed little or no effect against KB/MDR-TK tumors. Ganciclovir inhibited the in vivo growth of KB/MDR-TK tumors almost completely under conditions that did not affect the growth of KB-3-1 tumors. Coadministration of vinblastine and ganciclovir inhibited the in vivo growth of KB/MDR-TK premixed with KB-3-1 at any ratio. Long-term, high-level expression of human P-glycoprotein was observed in peripheral blood cells of mice transplanted with Ha-MDR-IRES-TK-transduced bone marrow cells. Ganciclovir eliminated the P-glycoprotein-positive normal blood cells. However, no systemic toxicity was observed. These results clearly demonstrate that it is possible to use ganciclovir to treat MDR1-positive tumors that have been unintentionally transduced with Ha-MDR-IRES-TK. This safety-modified vector should be useful for introducing the MDR1 gene into bone marrow cells to protect normal cells from the toxic effects of cancer chemotherapy.

AU Sugimoto Y; Tsuruo T

SO Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K., (1997 Apr) Vol. 11 Suppl 3, pp. 552-6.

Journal code: 8704895. ISSN: 0887-6924. L-ISSN: 0887-6924.

TI In vivo drug-selectable markers in gene therapy.

AB Two-gene vectors with positive or positive-negative drug-selectable markers enable the expansion or elimination of genetically modified cells in vivo. We have established a bicistronic retroviral vector system which utilizes an internal ribosome entry site (IRES) to co-express two independent genes with high efficiency. As a positive-negative (suicide) marker, Herpes simplex virus thymidine

kinase was co-expressed with the human multidrug resistance gene, MDR1. Using this vector, almost all the MDR1-transduced cells showed hypersensitivity to a nucleoside analog, ganciclovir. As a dominant selectable marker, the MDR1 gene was co-expressed with alpha-galactosidase A for the model of gene therapy of Fabry disease. Vincristine selection efficiently enhanced the population of transduced cells expressing the second non-selectable genes. These drug-selectable retroviral vectors could be applicable to the therapy of many diseases.

- AU Sharma S; Miller P W; Stolina M; Zhu L; Huang M; Paul R W; Dubinett S M  
 SO Gene therapy, (1997 Dec) Vol. 4, No. 12, pp. 1361-70.  
 Journal code: 9421525. ISSN: 0969-7128. L-ISSN: 0969-7128.
- TI Multicomponent gene therapy vaccines for lung cancer: effective  
 eradication of established murine tumors in vivo with interleukin-7/herpes  
 simplex thymidine kinase-transduced autologous tumor and ex vivo activated  
 dendritic cells.
- AB Multiple antitumor modalities may be necessary to overcome lung  
 tumor-mediated immunosuppression and effectively treat non-small cell lung  
 cancer (NSCLC). To evaluate a multimodality gene therapy approach for  
 control of local tumor growth, a weakly immunogenic murine alveolar cell  
 carcinoma, L1C2, was transduced with either the  
 interleukin-7/hygromycin-herpes simplex thymidine kinase  
 (IL-7/HyHSVtk) internal ribosome entry site (IRES)  
 retroviral vector or a vector containing the HyHSVtk, but not the  
 IL-7 gene. Of the many cytokines available for gene transfer, IL-7 was  
 chosen for these studies because it both stimulates CTL responses and  
 down-regulates tumor production of the immunosuppressive peptide TGF-beta.  
 Following selection in hygromycin, IL-7 transduction was confirmed by  
 ELISA. Clones produced 1.25 to 10 ng of IL-7/ml/10(6) cells per 24 h. In  
 vitro, genetically modified tumor cells were significantly more sensitive  
 to ganciclovir (GCV) than unmodified parental tumor cells. The in vivo  
 growth of ex vivo modified L1C2 cells was evaluated. There was a  
 dose-response relationship between the amount of IL-7 secreted in vitro  
 and the growth of genetically modified murine tumor in vivo. Transduced  
 tumor cells regressed in mice following GCV therapy. Although ex vivo  
 gene modification of tumor cells led to complete resolution of the tumor  
 following implantation in vivo, IL-7 and HSVtk gene modified tumor cells  
 were not effective in treating established parental tumors. However when  
 5 x 10(5) bone marrow-derived, in vitro activated dendritic cells (DC)  
 were administered in combination with transduced tumor and GCV, 5 day old  
 established tumors were eradicated in 80% of mice. These studies suggest  
 that multicomponent vaccines may facilitate improved host responses by  
 replacing host immune deficits and thus could have a role in adjuvant  
 therapy and local control of NSCLC.